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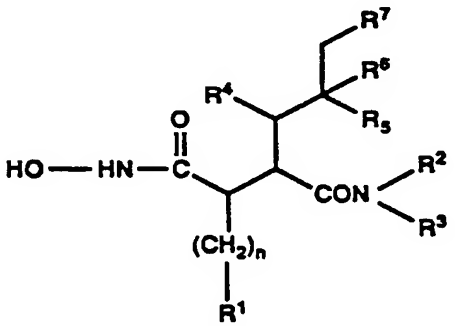
(71) Applicant: **F. HOFFMANN-LA ROCHE AG**
Postfach 3255
CH-4002 Basel(CH)

(72) Inventor: **Broadhurst, Michael John**
Ivy Cottage,
High Street
Barley, Royston, Herts.(GB)
Inventor: **Brown, Paul Anthony**
8 Periwinkle Lane
Hitchin, Herts.(GB)
Inventor: **Johnson, William Henry**
87 West Hill
Hitchin, Herts.(GB)
Inventor: **Lawton, Geoffrey**
Garden Fields,
Stevenage Road
St. Ippolitts, Hitchin, Herts(GB)

(74) Representative: **Mahé, Jean et al**
Postfach 3255
Grenzacherstrasse 124
CH-4002 Basel (CH)

(54) Hydroxamic acid derivatives as collagenase inhibitors.

(57) The invention provides hydroxamic acid derivatives of the formula



(I)

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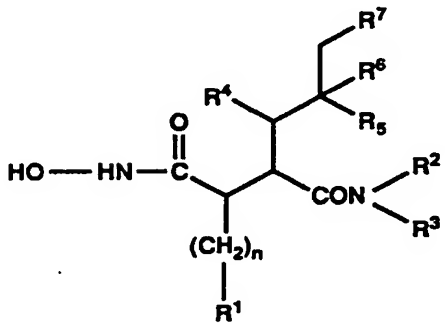
wherein R^1 represents a 5- or 6-membered N-heterocyclic ring, R^2 and R^3 each represent lower alkyl or NR^2R^3 represents a saturated 5-, 6- or 7-membered heterocyclic ring, R^4, R^5, R^6 and R^7 each represent hydrogen or methyl, provided that at least two of these symbols represent hydrogen and n stands for 1-4, and their pharmaceutically acceptable salts, which are collagenase inhibitors useful for the control or prevention of degenerative joint diseases such as rheumatoid arthritis and osteoarthritis or for the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

The present invention is concerned with hydroxamic acid derivatives.

The hydroxamic acid derivatives provided by the present invention are compounds of the general formula



(I)

wherein

R^1	represents a 5- or 6-membered N-heterocyclic ring which (a) is attached via the N atom, (b) optionally contains N, O and/or S as additional hetero atom(s) in a position or positions other than adjacent to the linking N atom, (c) is substituted by oxo on one or both C atoms adjacent to the linking N atom and (d) is optionally benz-fused or optionally substituted on one or more other C atoms by lower alkyl or oxo and/or on any additional N atom(s) by lower alkyl or aryl;
R^2	represents lower alkyl and R^3 represents lower alkyl or aryl, or
NR^2R^3	represents a saturated 5-, 6- or 7-membered heterocyclic ring which optionally contains $-NR^a$, -O-,-S-,-SO- or $-SO_2-$ as a ring member and/or which is optionally substituted by hydroxy, lower alkoxy, oxo, ketalized oxo, amino, mono(lower alkyl)-amino, di(lower alkyl)amino,carboxy, lower alkoxycarbonyl, hydroxymethyl, lower alkoxymethyl, carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl or hydroxyimino;
R^a	represents hydrogen, lower alkyl, lower alkanoyl, aryl-loweralkanoyl, lower alkoxycarbonyl, aryl-lower alkoxycarbonyl or mono(lower alkyl)carbamoyl;
R^4, R^5, R^6 and R^7	each represent hydrogen or methyl, provided that at least two of these symbols represent hydrogen; and

n stands for 1-4;

and pharmaceutically acceptable salts thereof.

The compounds of formula I possess valuable pharmacological properties. In particular, they are collagenase inhibitors and can be used in the control or prevention of degenerative joint diseases such as rheumatoid arthritis and osteoarthritis or in the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

Objects of the present invention are the compounds of formula I and their pharmaceutically acceptable salts per se and for use as therapeutically active substances; a process for the manufacture of said compounds and salts; intermediates useful in said process; medicaments containing said compounds and salts and the manufacture of these medicaments; and the use of said compounds and salts in the control or prevention of illnesses or in the improvement of health, especially in the control or prevention of degenerative joint diseases or in the treatment of invasive tumours or atherosclerosis, or for the manufacture of a medicament for the control or prevention of degenerative joint diseases or for the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

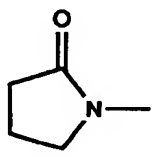
As used in this Specification, the term "lower alkyl", alone or in combination, means a straight-chain or branched-chain alkyl group containing a maximum of six, preferably one to four carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.butyl, isobutyl, tert.butyl, n-pentyl, n-hexyl and the like. The term "lower alkoxy", alone or in combination, means a straight-chain or branched-chain alkoxy group containing a maximum of six, preferably one to four carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert.butoxy and the like. The term "aryl" means phenyl which is optionally substituted by, for example, lower alkyl, lower alkoxy and/or halogen, i.e. fluorine, chlorine, bromine or iodine. The term "lower alkanoyl", alone or in combination, means an acyl group derived from an alkanoic acid containing up

to six carbon atoms, e.g. acetyl, propionyl, butyryl, isobutyryl and the like. A ketalized oxo group can be, for example, ethylenedioxy.

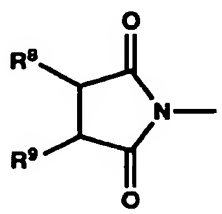
The compounds of formula I form pharmaceutically acceptable salts with bases such as alkali metal hydroxides (e.g. sodium hydroxide and potassium hydroxide), alkaline earth metal hydroxides (e.g. calcium hydroxide and magnesium hydroxide), ammonium hydroxide and the like. The compounds of formula I which are basic form pharmaceutically acceptable salts with acids. As such salts there come into consideration not only salts with inorganic acids such as hydrohalic acids (e.g. hydrochloric acid and hydrobromic acid), sulphuric acid, nitric acid, phosphoric acid etc, but also salts with organic acids such as acetic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, malic acid, salicylic acid, citric acid, methanesulphonic acid, p-toluenesulphonic acid etc.

The compounds of formula I contain at least two asymmetric carbon atoms and can accordingly exist as optically active enantiomers, as diastereoisomers or as racemates. The present invention is intended to embrace all of these forms.

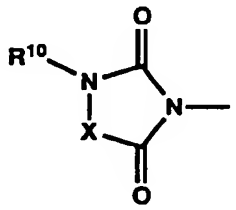
Compounds of formula I in which the N-heterocyclic ring R^1 optionally contains as additional hetero atom(s) one or two N atoms, one N atom and one O atom or one O atom are preferred. Especially preferred rings denoted by R^1 are those of the formulae:



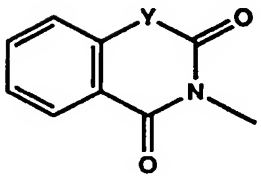
(a)



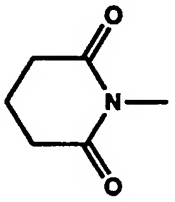
(b)



(c)

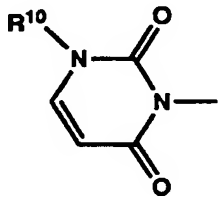


(d)



(e)

and



(f)

in which

R^8 and R^9	each represent hydrogen or together represent an additional bond or the remainder of a fused benzene ring;
R^{10}	represents hydrogen, lower alkyl or aryl;
X	represents -CO-, -CH_2-, -CH(lower alkyl)-, -C(lower alkyl)$_2$-, -NH-, -N(lower alkyl)- or -O-; and
Y	represents -O-, -NH- or -N(lower alkyl)-.

Examples of such rings are 2-oxo-1-pyrrolidinyl, 2,5-dioxo-1-pyrrolidino,phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl, 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, 2-methyl-3,5-dioxo-1,2,4-oxadiaxol-4-yl, 3-methyl-2,4,5-trioxo-1-imidazolidinyl, 2,5-dioxo-3-phenyl-1-imidazolidinyl and 2,6-dioxopiperidino. Those rings of formulae (b) and (c), especially phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl or 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl, are particularly preferred.

Compounds of formula I in which NR^2R^3 represents a 5-, 6- or 7-membered saturated heterocyclic ring as defined earlier are preferred. Such rings include 1-pyrrolidinyl, piperidino, 1-piperazinyl, 4-methyl-1-piperazinyl, hexahydro-1-pyridazinyl, morpholino, tetrahydro-1,4-thiazin-4-yl, tetrahydro-1,4-thiazin-4-yl 1-oxide, tetrahydro-1,4-thiazin-4-yl 1,1-dioxide and octahydro-1-azocinyl which can be substituted in the

manner even earlier; for example 2-(methylcarbamoyl)-1-pyrrolidinyl, 2-(hydroxymethyl)-1-pyrrolidinyl, 4-hydroxypiperidino, 2-(methylcarbamoyl)piperidino, 4-hydroxyiminopiperidino, 4-methoxypiperidino, 1,4-dioxa-8-azaspiro-[4.5]decan-8-yl, hexahydro-3-(methylcarbamoyl)-2-pyridazinyl and hexahydro-1-(benzyloxycarbonyl)-2-pyridazinyl. Compounds of formula I in which NR^2R^3 represent a 6-membered saturated heterocyclic ring, particularly morpholino, tetrahydro-1,4-thiazin-4-yl, 4-hydroxypiperidino or hexahydro-3-(methylcarbamoyl-2-pyridazinyl, are especially preferred.

Compounds of formula I in which R^4, R^5 and R^7 each represent hydrogen and R^6 represents methyl are also preferred.

Further, compounds of formula I in which n stands for 1 or 2 are preferred.

The most preferred compounds of formula I are:

4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimido-ethyl]-4-methylvaleryl]morpholine,

4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimido-ethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine,

1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimido-ethyl]-4-methylvaleryl]-4-piperidinol,

1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleryl]-piperidine,

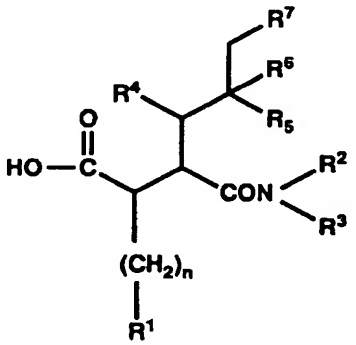
4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-tetrahydro-1,4-thiazine,

hexahydro-2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimido-ethyl]-4-methylvaleryl]-N-methyl-3(S)-pyridazinecarboxamide and

1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol.

According to the process provided by the present invention, the compounds of formula I and their pharmaceutically acceptable salts are manufactured by

(a) reacting an acid of the general formula



(II)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and n have the significance given earlier,

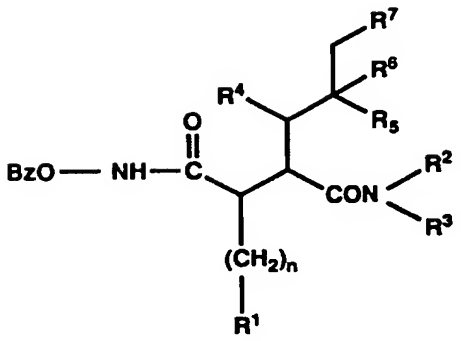
with a compound of the general formula

$H_2N\text{-}OZ$ (III)

wherein Z represents hydrogen, tri(lower alkyl)silyl or diphenyl(lower alkyl)silyl,

and, where required, cleaving off any diphenyl(lower alkyl)silyl group present in the reaction product, or

(b) catalytically hydrogenating a compound of the general formula



(IV)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and n have the significance given earlier and Bz represents benzyl,

and,

if desired, converting a compound of formula I obtained into a pharmaceutically acceptable salt.

The reaction of an acid of formula II with a compound of formula III in accordance with embodiment (a) of the process can be carried out in a known manner, for example in an inert organic solvent such as dimethylformamide or the like using hydroxybenzotriazole in the presence of a condensation agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride at about 0°C to about room temperature. Preferred compounds of formula III are those in which Z represents hydrogen, tert.butyl-dimethylsilyl or tert.butyldiphenylsilyl. When a compound of formula III in which Z represents tri(lower alkyl)silyl is used, this group is cleaved off during the reaction and working-up, and a compound of formula I is obtained directly. On the other hand, when a compound of formula III in which Z represents diaryl-(lower alkyl)silyl is used, this group remains in the reaction product and must subsequently be cleaved off in a known manner, for example by means of fluoride ions.

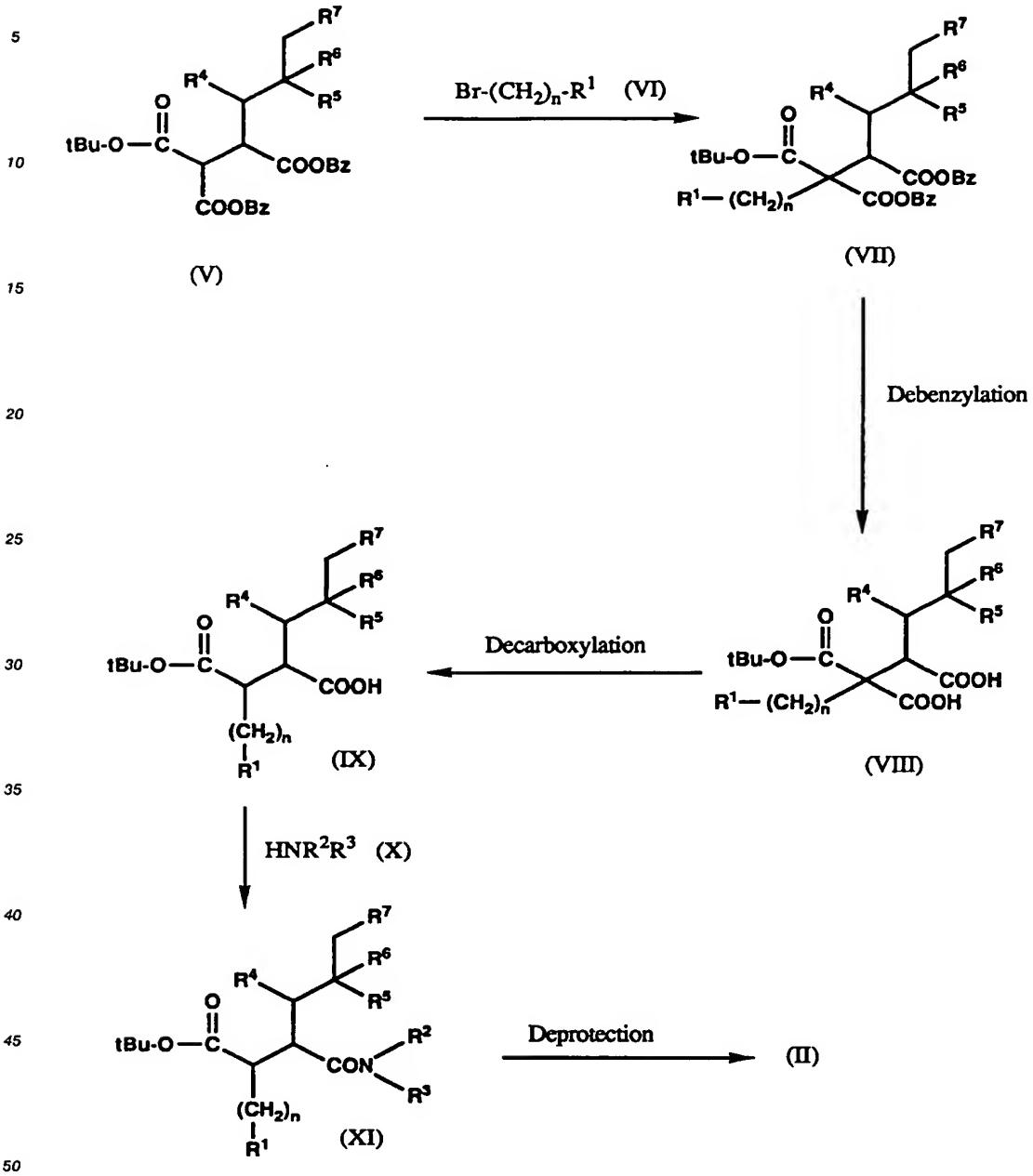
The catalytic hydrogenation of a compound of formula IV in accordance with embodiment (b) of the process can be carried out in a manner known per se; for example in an inert organic solvent using hydrogen in the presence of a noble metal catalyst. Suitable inert organic solvents are, for example, lower alkanols such as methanol, ethanol, etc. With respect to the catalyst, this can be, for example, a platinum, palladium or rhodium catalyst which can be supported on a suitable carrier material. Palladium-on-charcoal is the preferred catalyst. The temperature and pressure are not critical, although for convenience the catalytic hydrogenation is preferably carried out at room temperature and under atmospheric pressure.

Compounds of formula I can be converted into pharmaceutically acceptable salts by treatment with bases and basic compounds of formula I can be converted into pharmaceutically acceptable salts by treatment with acids. Such treatments can be carried out in a conventional manner.

The acids of formula II which are used as starting materials in embodiment (a) of the process are novel and form a further object of the present invention.

The acids of formula II can be prepared, for example, as illustrated in the following Reaction Scheme in which R^1, R^2, R^3, R^4, R^5, R^6, R^7, Bz and n have the significance given earlier and tBu represents tert.butyl.

Reaction Scheme



Having regard to the foregoing Reaction Scheme, in the first step an alkanetricarboxylate of formula V is reacted with a bromoalkyl-substituted N-heterocycle of formula VI to give a compound of formula VII. This reaction can be carried out in a generally known manner, for example by treating the alkane-tricarboxylate in an inert organic solvent such as dimethyl-formamide with a strong base, e.g. an alkali metal hydride such as sodium hydride, subsequently adding the bromoalkyl-substituted N-heterocycle and then allowing the reaction to proceed, preferably at room temperature.

The compound of formula VII obtained is then debenzylated to a compound of formula VIII in a manner known per se, for example by hydrogenation in an inert organic solvent, e.g. a lower alkanol such as methanol or ethanol, in the presence of a catalyst such as palladium-on-charcoal.

The subsequent decarboxylation of a compound of formula VIII to a compound of formula IX is also carried out in a known manner, for example by heating in an aromatic solvent such as benzene or toluene in the presence of a base such as N-methylmorpholine.

In the next step a compound of formula IX is reacted with an amine of formula X to give a compound of formula XI. This reaction can be carried out in a manner known per se. For example, the reaction is conveniently carried out in an inert organic solvent such as dimethylformamide or the like using hydroxybenzotriazole in the presence of a condensation agent such as 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride or by converting the compound of formula IX with oxalyl chloride into the corresponding chloride and reacting this with the amine, expediently in the presence of a base such as triethylamine at about 0-25 °C.

In the final step, a compound of formula XI is deprotected to give a desired acid starting material of formula II. This deprotection can be carried out in a manner known per se, for example by treatment with trifluoroacetic acid.

If desired, a compound of formula XI can be functionally modified prior to the deprotection step. Thus, for example, a compound of formula XI in which NR^2R^3 represents a saturated 5-, 6- or 7-membered heterocyclic ring containing -S- as a ring member can be oxidized in a known manner, e.g. using a peracid such as m-chloroperbenzoic acid, to a corresponding compound which contains -SO- or $-SO_2-$ as a ring member.

The compounds of formula IV which are used as starting materials in embodiment (b) of the process are novel and form a further object of the present invention.

The compounds of formula IV can be prepared, for example, by reacting an acid of formula II with O-benzylhydroxylamine. This reaction can be carried out in a known manner, for example in an inert organic solvent such as dimethylformamide using hydroxybenzotriazole in the presence of a condensation agent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

The remaining compounds which are used as intermediates or reactants in the manufacture of the compounds of formula I are known compounds or analogues of known compounds which can be prepared in a similar manner to the known compounds.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable salts are collagenase inhibitors. The in vitro collagenase inhibiting activity of the present compounds and salts can be demonstrated using collagenase obtained from a culture of human synovial fibroblasts according to the method of Dayer J-M et al., Proc. Natl. Acad. Sci. USA (1976), 73 945, following activation of the procollagenase in the conditioned medium by treatment with trypsin. Collagenase activity was measured using ^{14}C-acetylated collagen type I from rat tail tendons as the substrate and employing the microtitre plate assay method of Johnson-Wint, B, Anal. Biochem. (1980), 104, 175. The IC_{50} is that concentration of a compound or salt of the present invention in the enzyme digestion which reduces substrate cleavage and solubilization to 50% of that achieved by the enzyme alone.

The results obtained in the foregoing test with representative compounds and salts of this invention are compiled in Table I hereinafter:

Table I

Compound of formula I	IC_{50} (nM)
A	10
B	6
C	5
D	15
E	7
F	1.2
G	6.9

Compound A: 4-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]morpholine.

Compound B: 4-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine.

Compound C: 1-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-4-piperidinol.

Compound D: 1-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleryl]piperidine.

Compound E: 4-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine.

Compound F: Hexahydro-2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-N-methyl-3(S)-pyridazine- carboxamide.

Compound G: 1-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol

The compounds of formula I and their pharmaceutically acceptable salts can be used as medicaments, for example in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, they can also be administered rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

For the manufacture of pharmaceutical preparations the compounds of formula I and their pharmaceutically acceptable salts can be formulated with therapeutically inert, inorganic or organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active ingredient no carriers are, however, generally required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose and the like. Suitable carriers for the manufacture of injection solutions are, for example, water, alcohols, polyols, glycerine, vegetable oils and the like. Natural and hardened oils, waxes, fats, semi-liquid polyols and the like are suitable carriers for the manufacture of suppositories.

The pharmaceutical preparations can also contain preservatives, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for adjustment of the osmotic pressure buffers coating agents or antioxidants.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically acceptable carrier as well as a process for the manufacture of such medicaments are also objects of the present invention. This process comprises mixing a compound of formula I or a pharmaceutically acceptable salt thereof with a therapeutically inert carrier material and bringing the mixture into a galenical administration form.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable salts can be used in the control or prevention of illnesses, especially in the control or prevention of degenerative joint diseases or in the treatment of invasive tumours, atherosclerosis or multiple sclerosis. The dosage can vary within wide limits and will, of course, be adjusted to the individual requirements in each particular case. In

general, in the case of administration to adults, a daily dosage of from about 5 mg to about 30 mg, preferably from about 10 mg to about 15 mg, should be appropriate, although the upper limit may be exceeded when this is found to be expedient. The daily dosage can be administered as a single dosage or in divided dosages.

The following Examples illustrate the present invention in more detail. In these Examples all temperatures are given in degrees Celsius.

Example 1

A solution of 0.15 g of 1-[2(R))-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]pyrrolidine (diastereoisomer 1) in 3 ml of dry dimethylformamide was cooled to 0°C while stirring under nitrogen and treated successively with 0.075 g of 1-hydroxybenzotriazole, 0.12 g of O-(tert.butyldimethylsilyl)-hydroxylamine, 0.075 ml of N-methylmorpholine and 0.094 g of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride. The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was evaporated and the residue was treated with 5 ml of 5% aqueous sodium hydrogen carbonate solution. The product was extracted with three portions of ethyl acetate and the combined extracts were washed with 1.0M hydrochloric acid and aqueous sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated and the residue was triturated with a mixture of ether and hexane. The solid was filtered off and dried to give 0.09 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]pyrrolidine (diastereoisomer 1) in the form of a white powder: nmr (MeOD): 7.84-7.71 (m,4H); 3.78-3.70 (m.3H); 3.54-3.43 (m,1H); 3.23-3.15 (m,1H); 3.05-2.90 (m,3H); 2.06-1.86 (m,2H); 1.83-1.71 (m,2H), 1.58-1.49 (m,1H); 1.43-1.32 (m,1H); 1.23-1.14 (m,1H); 0.87 (d,3H,J = 6); 0.81 (d,3H,J = 6); MS 402 $(M + H)^+$.

The starting material was prepared as follows:

(i) A solution of 0.41 g of an approximately 6:1 mixture of diastereoisomer 1 and diastereoisomer 2 of 2-(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleric acid in 5 ml of dry dimethylformamide was cooled to 0°C while stirring under nitrogen and treated successively with 0.16 g of 1-hydroxybenzotriazole, 0.1 g of pyrrolidine, 0.13 ml of N-methylmorpholine and 0.23 g of 1-ethyl-3-(3-dimethylamino propyl)carbodiimide hydrochloride. The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was evaporated and the residue was treated with 20 ml of 5% aqueous sodium hydrogen carbonate solution. The product was extracted with three portions of ethyl acetate and the combined extracts were washed with 5% citric acid and aqueous sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated to give 0.5 g of a colourless gum which was purified by flash chromatography on silica gel using hexane/ethyl acetate (5:4) for the elution. After elution of the faster moving product (diastereoisomer 2) there was obtained 0.365 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl)-4-methylvaleryl]pyrrolidine (diastereoisomer 1) in the form of a colourless gum; nmr (MeOD): 7.88-7.79 (m,4H); 3.99-3.93 (m,1H); 3.78-3.66 (m,2H); 3.60-3.53 (m,1H); 3.39-3.30 (m,1H); 3.27-3.21 (m,1H); 3.19-3.13 (m,1H); 3.06-2.99 (m,1H); 2.10-1.96 (m,2H); 1.92-1.83 (m,2H); 1.76-1.68 (m,1H) 1.53-1.42 (m,1H), 1.33 (s,9H); 1.30-1.20 (m,1H); 0.95 (d,3H,J = 6); 0.88 (d,3H,J = 6).

(ii) A solution of 0.35 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl)-4-methylvaleryl]-pyrrolidine (diastereoisomer 1) in 10 ml of dichloromethane was treated with 3 ml of trifluoroacetic acid. The mixture was stirred at room temperature for 2 hours and 10 ml of toluene were added. The solvent was evaporated and the residue was reevaporated a further three times with 20 ml portions of toluene. The residue was crystallized from ether to give 0.161 g of 1-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]-pyrrolidine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.86-7.75 (m,4H); 3.92 (dd,1H,J = 11,6); 3.80 (dd,1H, J = 11,6); 3.74-3.67 (m,1H); 3.55-3.46 (m,1H); 3.32-3.18 (m,2H); 3.13-2.99 (m,2H); 2.06-1.90 (m,2H); 1.87-1.77 (m,2H); 1.71-1.62 (m,1H): 1.52-1.40 (m,1H); 1.33-1.25 (m,1H); 0.92 (d,3H,J = 6); 0.86 (d,3H,J = 6); MS: 387 $(M + H)^+$.

Example 2

In a manner analogous to that described in the first paragraph of Example 1, from 0.155 g of 1-[2(R)-[1-(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]piperidine (diastereoisomer 1), prepared in a manner analogous to that described in Example 1(i)-(ii), there was obtained 0.1 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methyl valeryl]piperidine (diastereoisomer 1) in the form of a white powder; nmr (MeOD): 7.88-7.76 (m,4H); 3.89 (dd,1H,J = 11,6); 3.86-3.77 (m,1H); 3.70-3.58 (m,3H); 3.37-3.24 (m,2H); 2.99-2.93 (m,1H); 1.78-1.53 (m,6H); 1.52-1.36(m,2H); 1.23-1.14 (m,1H); 0.93-0.85 (m,6H);

MS: 416 $(M+H)^+$.

Example 3

In a manner analogous to that described in the first paragraph of Example 1, from 0.283 g of 4-[2(R)-[1-(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]morpholine (diastereoisomer 1), prepared in a manner analogous to that described in Example 1(i)-(ii), there was obtained 0.12 g of 4-[2-(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) in the form of a white powder; nmr (MeOD): 7.87-7.76 (m,4H); 3.87 (dd,1H,J = 11,6); 3.83-3.70 (m,3H); 3.68-3.60 (m,3H); 3.59-3.51 (m,2H); 3.47-3.39 (m,1H); 3.32-3.23 (m,1H); 2.99-2.92 (m,1H); 1.66-1.58 (m,1H); 1.47-1.36 (m,1H); 1.24-1.14 (m,1H); 0.91-0.84 (m,6H); MS: 418 $(M+H)^+$.

Example 4

In a manner analogous to that described in the first paragraph of Example 1, from 0.16 g of 1-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]hexahydroazepine (diastereoisomer 1), prepared in a manner analogous to that described in Example 1(i)-(ii), there was obtained 0.13 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]hexahydroazepine (diastereoisomer 1) in the form of a white powder; nmr (MeOD); 7.88-7.76 (m,4H); 3.95 (dd,1H,J = 11,6); 3.84-3.76 (m,1H); 3.70-3.54 (m,3H); 3.37-3.25 (m,2H); 2.97-2.89 (m,1H); 1.94-1.77 (m,2H); 1.75-1.53 (m,7H); 1.51-1.40 (m,1H); 1.27-1.19 (m,1H); 0.92 (d,3H,J = 6); 0.88 (d,3H,J = 6); MS: 430 $(M+H)^+$.

Example 5

In a manner analogous to that described in the first paragraph of Example 1, from 0.28 g of 4-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine (diastereoisomer 1), prepared in a manner analogous to that described in Example 1(i)-(ii), there was obtained 0.14 g of 4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.84-7.73 (m,4H); 4.09-4.01 (m,1H); 3.93-3.81 (m,3H); 3.63-3.53 (m,2H); 3.29-3.21 (m,1H); 2.95-2.87 (m,1H); 2.76-2.69 (m,1H); 2.67-2.59 (m,1H); 2.57-2.46 (m,2H); 1.63-1.55 (m,1H); 1.43-1.32 (m,1H); 1.20-1.12 (m,1H); 0.86 (d,3H,J = 6); 0.83 (d,3H,J = 6); MS: 434 $(M+H)^+$.

Example 6

In a manner analogous to that described in the first paragraph of Example 1, from 0.36 g of 1-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1), prepared in a manner analogous to that described in Example 1(i)-(ii), there was obtained, after purification of the crude product by flash chromatography on silica gel using dichloromethane/methanol (16:1) for the elution, 0.053 g of 1-[2-(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1) in the form of a white powder; nmr (MeOD): 7.88-7.76 (m,4H); 4.15-3.79 (m,4H); 3.67-2.84 (m,5H); 2.06-1.73 (m,2H); 1.70-1.14 (m,5H); 0.95-0.84 (m,6H); MS: 432 $(M+H)^+$.

Example 7

In a manner analogous to that described in Example 1, from 0.557 g of 2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-N,N,4-trimethylvaleramide (diastereoisomer 1), prepared in a manner analogous to that described in Example 1(i)-(ii), there was obtained, after purification of the product by flash chromatography using 2% methanol in dichloromethane for the elution, 0.053 g of 2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-N,N,4-trimethylvaleramide in the form of a white solid; nmr (MeOD): 7.85-7.75 (m,4H); 3.84 (dd,J = 14,7,1H); 3.68 (dd,J = 14,10,1H); 3.18 (s,3H); 2.98-2.93 (m,1H); 2.75 (s,3H); 1.6-1.53 (m,1H); 1.4-1.3 (m,1H); 1.23-1.14 (m,1H); 0.88 (d,J = 8,3H); 0.84 (d,J = 8,3H). MS: 376 $(M+H)^+$.

Example 8

In a manner analogous to that described in the first paragraph of Example 1, from 0.59 g of an approximately 6:1 mixture of diastereoisomer 1 and diastereoisomer 2 of N^2-[2(R)-[1(R or S)-carboxy-2-phthal imidoethyl]-4-methylvaleryl]-N^1-methyl-L-prolinamide, prepared in a manner analogous to that described in Example 1(i)-(ii), there was obtained, after crystallization of the product from a mixture of

dichloromethane and ether, 0.12 g of diastereoisomer 1 of N^2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-N^1-methyl-L-prolinamide in the form of a white solid; nmr (MeOD): 7.86-7.75 (m,4H); 4.12-4.07 (m,1H); 3.92-3.83 (m,2H); 3.74-3.64 (m,2H); 3.13-3.04 (m,1H); 2.93-2.86 (m,1H); 2.67 (s,3H); 2.19-1.96 (m,3H); 1.91-1.82 (m,1H); 1.75-1.65 (m,1H); 1.64-1.55 (m,1H); 1.23-1.14 (m,1H); 0.93 (d,3H,J = 6); 0.86 (d,3H,J = 6); MS: 458 $(M)^+$.

Example 9

In a manner analogous to that described in the first paragraph of Example 1, except that the reaction was only allowed to proceed for 3 hours, from 0.31 g of 1-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]-2(S)-pyrrolidinemethanol (diastereoisomer 1) there was obtained, after purification of the product by flash chromatography using dichloromethane/methanol (12:1) for the elution and crystallization from a mixture of ethyl acetate and ether, 0.06 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-2(S)-pyrrolidinemethanol (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.88-7.77 (m,4H); 3.86-3.73 (m,4H); 3.63-3.50 (m,2H); 3.98-3.27 (m,1H); 3.10-2.92 (m,2H); 2.07-1.83 (m,4H); 1.62-1.43 (m,2H); 1.28-1.17 (m,1H); 0.97-0.83 (m,6H); MS: 432 $(M + H)^+$.

The starting material was prepared as follows:

A solution of 0.355 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]-2-(S)-pyrrolidinemethanol (diastereoisomer 1), prepared in a manner analogous to that described in Example 1(i), in 7 ml of toluene was treated with 0.07 g of 3-methyl-3-pentenol and 0.7 ml of trimethylsilyl bromide. The mixture was stirred under a dry nitrogen atmosphere for 1.5 hours and then the solvent was evaporated. After three further evaporations from 10 ml of toluene each time there was obtained 0.31 g of a pale brown foam containing 1-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]-2(S)-pyrrolidinemethanol (diastereoisomer 1) which was used without further purification.

Example 10

In a manner analogous to that described in the first paragraph of Example 1, from 0.568 g of an approximately 6:1 mixture of diastereoisomer 1 and diastereoisomer 2 of 1-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]-4-methylpiperazine hydrobromide, prepared in a manner analogous to that described in Example 9(i), there was obtained, after purification of the product by flash chromatography on silica gel using dichloromethane/methanol (12:1) for the elution and precipitation of the hydrochloride by the addition of hydrogen chloride in ethyl acetate, 0.105 g of 1-[2(R)-1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-4-methylpiperazine hydrochloride (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.89-7.79 (m,4H); 4.18-3.80 (m,4H); 3.74 (dd,1H,J = 11,5); 3.48-3.18 (br m,6H); 2.93-2.84 (m,4H); 1.76-1.67 (m,1H); 1.52-1.42 (m,1H), 1.35-1.27 (m,1H); 0.93 (d,3H,J = 6); 0.89 (d,3H,J = 5.5); MS: 431 $(M + H)^+$.

Example 11

In a manner analogous to that described in the first paragraph of Example 1, from 0.29 g of 4-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine 1,1-dioxide (diastereoisomer 1), there was obtained 0.13 g of 4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-tetrahydro1,4-thiazine 1,1-dioxide (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.88-7.75 (m,4H); 4.33-4.23 (m,1H); 4.20-4.04 (m,2H); 3.93 (dd,1H,J = 11,6); 3.87-3.78 (m,1H); 3.73 (dd,1H,J = 11,5); 3.44-3.28 (m,3H); 3.22-3.03 (m,3H); 2.97-2.90 (m,1H); 1.67-1.57 (m,1H); 1.51-1.38 (m,1H); 1.34-1.25 (m,1H); 0.93-0.84 (m,6H); MS: 466 $(M + H)^+$.

The starting material was prepared as follows:

(i) A solution of 0.3 g of 4-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]-tetrahydro-1,4-thiazine (diastereoisomer 1) in 20 ml of dichloromethane was cooled to 0 °C and treated with 0.3 g of 85% m-chloroperoxybenzoic acid. The mixture was stirred at ambient temperature overnight and then the solution was washed twice with 5% aqueous sodium hydrogen carbonate solution, dried over anhydrous magnesium sulphate and evaporated to give a white foam. After purification by flash chromatography on silica gel using ethyl acetate/hexane (2:3) for the elution there was obtained 0.33 g of 4-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]-tetrahydro-1,4-thiazine 1,1-dioxide (diastereoisomer 1) in the form of a white foam which solidified to a white solid; nmr (MeOD); 7.89-7.78 (m,4H); 4.36-4.23 (m,2H); 4.11 (dd,1H,J = 11,7); 4.07-3.98 (m,1H); 3.85-3.73 (m,2H); 3.44-3.18 (m,2H); 3.21-3.05 (m,4H); 1.73-1.64 (m,1H); 1.61-1.59 (m,1H); 1.40-1.32 (m,1H); 1.28 (s,9H); 0.95-0.88

(m,4H).

(ii) In a manner analogous to that described in Example 1(ii), from 0.33 g of 4-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine 1,1-dioxide (diastereoisomer 1) there was obtained 0.29 g of 4-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine 1,1-dioxide (diastereoisomer 1) in the form of a white foam which was used without further purification.

Example 12

In a manner analogous to that described in the first paragraph of Example 1, from 0.3 g of 8-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]-1,4-dioxa-8-azaspiro[4.5]decane (diastereoisomer 1) prepared in a manner analogous to that described in Example I(i)-(ii), there was obtained, after purification of the product by flash chromatography on silica gel using ethyl acetate/methanol (200:5) for the elution, 0.105 g of 8-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-1,4-dioxa-8-azaspiro[4.5]-decane (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.87-7.75 (m,4H); 3.97 (m,4H); 3.91-3.81 (m,2H) 3.79-3,60 (m,3H); 3.45-3.26 (m,2H); 3.00-2.91 (m,1H); 1.89-1.80 (m,1H); 1.74-1.51 (m,4H); 1.45-1.31 (m,1H); 1.23-1.13 (m,1H); 0.88 (d,3H,J = 6); 0.85 (d,3H,J = 5.5); MS: 474 $(M+H)^+$.

Example 13

A solution of 0.13 g of 1-[2(R)-[1(R or S)-(benzyioxycarbamoyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in 7.0 ml of methanol was hydrogenated in the presence of 40 mg of 10% palladium-on-charcoal for 30 minutes. The catalyst was removed by filtration and the solution was evaporated to give 0.076 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 3.81-3.72 (m,2H); 3.67 (dd,1H,J = 11,7); 3.64-3.55 (m,1H); 3.44 (dd,1H,J = 11,5); 3.39-3.23 (m,2H); 3.11 (s,6H); 2.96-2.88 (m,1H); 1.77-1,33 (m,8H); 1.19-1.11 (m,1H); 0.87 (d,3H,J = 6); 0.85 (d,3H,J = 6); MS: 398 $(M+H)^+$.

The starting material was prepared as follows:

(i) 0.284 g of 60% sodium hydride was added to a stirred ice-cold solution of 3.01 g of 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2(R)-pentanetricarboxylate in 50 ml of dry dimethylformamide under a nitrogen atmosphere. The mixture was stirred for 30 minutes at 0° and for a further 1.5 hours at ambient temperature, and again cooled to 0° before the addition of 1.6 g of 4-bromomethyl-1,2-dimethylurazole. The mixture was allowed to return to ambient temperature and was stirred for 3 hours. The volatiles were evaporated under high vacuum and the residue was dissolved in ethyl acetate and washed with 5% aqueous citric acid solution, water and saturated sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated and the residue was purified by flash chromatography on silica gel using hexane/ether (1:1) followed by ether for the elution. There were obtained 2.464 g of 1,2-dibenzyl 1-tert.butyl 4-methyl-1-[(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)methyl]-1,1,2(R)-pentanetricarboxylate in the form of a colourless oil.

(ii) 2.464 g of 1,2-dibenzyl 1-tert.butyl 4-methyl-1-[(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)methyl]-1,1,2(R)-pentanetricarboxylate were dissolved in 40 ml of methanol containing 0.25 g of 10% palladium-on-charcoal catalyst. The mixture was hydrogenated for 2 hours, the catalyst was removed by filtration and the solvent evaporated to give 1-(tert.butoxycarbonyl)-4-methyl-1-[(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)methyl]-1,2(R)-pentanedicarboxyic acid in the form of a colourless gum. This was dissolved in 60 ml of toluene containing 0.43 ml of N-methylmorpholine and the mixture was heated under reflux for 1 hour. The solution was washed with 5% aqueous citric acid solution, water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulphate and evaporated to give 1.422 g of 2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleric acid in the form of a waxy solid as an approximately 6:1 mixture of diastereoisomer 1 and diastereoisomer 2.

(iii) In a manner analogous to that described in Example(i) from 0.831 g of an approximately 6:1 mixture of diastereoisomer 1 and diastereoisomer 2 of 2(R)-[1(R or S)-(tert.butoxycarbonyl)]-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleric acid there was obtained 0.462 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a colourless oil.

(iv) A solution of 0.462 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in 7 ml of dichloromethane was

treated with 0.85 ml of trifluoroacetic acid. The mixture was stirred at room temperature for 1.5 hours and then toluene was added and the solvents were evaporated. After a further three evaporations from toluene the residue was dissolved in 11 ml of dry dimethylformamide, cooled to 0° and stirred under nitrogen during successive additions of 0.13 g of O-benzylhydroxylamine, 0.152 g of 1-hydroxybenzotriazole, 0.25 ml of N-methylmorpholine and 0.208 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was evaporated and the residue was treated with 5% aqueous sodium hydrogen carbonate solution. The product was extracted with ethyl acetate and the ethyl acetate extract was washed with 5% citric acid solution and aqueous sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated and the residue was purified by flash chromatography on silica gel using ethyl acetate for the elution. In addition to 0.14 g of recovered starting material there was obtained 0.142 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of white solid; nmr ($CDCl_3$): 9.77 (s,1H); 7.44-7.29 (m,5H); 4.90 (q,2H, J = 8); 3.78 (dd,1H,J = 11,5); 3.70-3.63 (m,2H); 3.62-3.53 (m,1H); 3.49-3.42 (m,1H); 3.41-3.33 (m,1H); 3.28-3.22 (m,1H); 3.10 (s,6H); 3.00-2.93 (m,1H); 1.81-1.38 (m,8H); 1.29-1.23 (m,1H); 0.88 (d,3H,J = 6); 0.85 (d,3H,J = 6).

Example 14

In a manner analogous to that described in the first paragraph of Example 13, from 0.182 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(2,6-dioxopiperidino)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) there was obtained 0.066 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(2,6-dioxopiperidino)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 4.06 (dd,1H,J = 11,6.5); 3.80-3.57 (m,4H); 3.53-3.46 (m,1H); 3.34-3.24 (m,1H)); 2.68-2.54 (m,5H); 1.92-1.82 (m,2H); 1.76-1.45 (m,7H); 1.44-1.32 (m,1H); 1.14-1.06 (m,1H); 0.87 (d,3H,J = 6); 0.83 (d,3H,J = 6); MS: 382 $(M = H)^+$.

The starting material was prepared as follows:

(i) In a manner analogous to that described in Example 13(i)-(iii), from 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2(R)-pentanetricarboxylate and N-bromomethylglutarimide there was obtained 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(2,6-dioxopiperidine)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a colourless gum.

(ii) A solution of 0.324 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(2,6-dioxopiperidino)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in 6.5 nil of toluene was treated with 0.065 g of 3-methyl-3-pentanol and 0.65 ml of trimethylsilyl bromide. The mixture was stirred under a dry nitrogen atmosphere for 1 hour and then the solvent was evaporated. After three further evaporations from toluene the residue was dissolved in 10 ml of dry dimethylformamide, cooled to 0° and stirred under nitrogen during successive additions of 0.095 g of O-benzylhydroxylamine, 0.111 g of 1-hydroxybenzotriazole 0.18 ml of N-methylmorpholine and 0.152 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. The mixture was allowed to warm to room temperature and was stirred overnight. The solvent was evaporated and the residue was treated with 5% aqueous sodium hydrogen carbonate solution. The product was extracted with ethyl acetate and the ethyl acetate extract was washed with 5% citric acid solution and aqueous sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated and the residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (7:2) for the elution. There was obtained 0.182 g of 1-[2(R)-[1(R or S)-(benxyloxycarbamoyl)-2-(2,6-dioxo piperidino)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a white solid; nmr ($CDCl_3$): 9.23 (s,1H); 7.46-7.31 (m,5H); 4.96-4.88 (m,2H): 3.98 (dd,1H,J = 11,5); 3.89-3.76 (m,2H); 3.74-3.64 (m,1H); 3.52-3.42 (m,1H); 3.33-3.21 (m,2H); 2.76-2.67 (m,1H); 2.63-2.52 (m,4H); 1.94-1.37 (m,10H); 1.24-1.14 (m,1H); 0.88 (d,3H,J = 6); 0.84 (d,3H,J = 6).

Example 15

In a manner analogous to that described in the first paragraph of Example 13, from 0.39 g of 1-[2(R)-[1-(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methyivaleryl]piperidine (diastereoisomer 1) there was obtained 0.255 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 3.84-3.63 (m,4H); 3.49-3.41 (m,1H); 3.38-3.25 (m,2H); 2.90-2.83 (m,4H); 1.80-1.28 (m,14H); 1.19-1.11 (m,1H); 0.89 (d,3H,J = 5.5); 0.86 (d,3H,J = 5.5); MS: 411 $(M + H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 14(i)-(ii), from 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2(R)-pentanetricarboxylate and 3-bromomethyl-1,5,5-trimethylhydantoin, there was obtained 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a white foam; nmr ($CDCl_3$): 9.50 (brs,1H); 7.45-7.39 (m,5H); 3.79-3.56 (m,4H); 3.52-3.42 (m,1H) 3.33-3.23 (m,2H); 2.94-2.80 (m,4H); 1.93-1.29 (m,14H); 1.26-1.16 (m,1H); 0.87 (d,3H,J = 6); 0.84 (d,3H,J = 6).

Example 16

In a manner analogous to that described in the first paragraph of Example 13, from 0.335 g of 4-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)-ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) there was obtained 0.198 g of 4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 3.78 (s,2H); 3.73-3.45 (m,9H); 3.36 (dd, 1H, J = 11,5); 3.18-3.10 (m,1H); 2.85 (s,3H); 2.82-2.75 (m,1H); 1.57-1.47 (m,1H); 1.38-1.26 (m,1H); 1.14-1.05 (m,1H); 0.82-0.75 (m,6H); MS: 385 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 15(i)-(ii), from 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2(R)-pentanetricarboxylate and 3-bromomethyl-1-methylhydantoin there was obtained 4-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) in the form of a white solid; MS: 475 $(M+H)^+$.

Example 17

In a manner analogous to that described in the first paragraph of Example 1, from 0.273 g of 1-[2(R)-[1-(R or S)-carboxy-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) there was obtained 0.023 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)-ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a white solid; nmr (MeOD); 3.78 (s,2H); 3.74-3.64 (m,2H); 3.63-3.48 (m,2H); 3.35-3.26 (m,2H); 3.25-3.15 (m,1H); 2.85 (s,3H); 2.82-2.73 (m,1H); 1.68-1.25 (m,8H); 1.10-1.03 (m,1H); 0.82 (d,3H,J = 6); 0.75 (d,3H,J = 6); MS: 383 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(ii), from 0.325 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(3-methyl-2,5-dioxo-1-imidasolidinyl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1), prepared in a manner analogous to that described in Example 13(i)-(iii) from 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2(R)-pentanetricarboxylate and 3-bromomethyl-1-methylhydantoin, there was obtained 0.273 g of 1-[2(R)-[1(R or S)-carboxy-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a colourless gum which was used without further purification.

Example 18

In a manner analogous to that described in the first paragraph of Example 1, from 0.45 g of 4-[2(R)-[1(R or S)-carboxy-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine (diastereoisomer 1) there was obtained 0.155 mg of 4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 4.09-3.88 (m,3H); 3.86 (s,2H); 3.78-3.70 (m,1H); 3.66 (dd,1H,J = 11,7); 3.42 (dd, 1H, J = 11,5); 3.29-3.21 (m,1H); 2.92 (s,3H); 2.88-2.82 (m,1H); 2.78-2.71 (m,1H); 2.68-2.54 (m,3H); 1.65-1.57 (m,1H); 1.46-1.34 (m,1H); 1.22-1.15 (m,1H); 0.90-0.84 (m,6H); MS: 401 $(M+H)^+$.

The starting material was prepared as follows:

(i) In a manner analogous to that described in Example 13(i)-(iii), from 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2(R)-pentanetricarboxylate and 3-bromomethyl-1-methylhydantoin there was obtained 4-[2(R)-[1-(R or S)-(tert.butoxycarbonyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 3.98-3.84 (m,6H); 3.77 (dd,1H,J = 11,7); 3.47 (dd,1H, J = 11,5); 3.22-3.14 (m,1H); 3.09-3.03 (m,1H); 2.95 (s,3H); 2.81-2.73 (m,1H); 2.69-2.55 (m,3H); 1.77-1.68 (m,1H); 1.53-1.39 (m,10H); 1.26-1.18 (m,1H); 0.94-0.86 (m,6H).

(ii) A solution of 0.52 g of 4-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)-ethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine (diastereoisomer 1) in 15 ml of dichloromethane was treated with 1.05 nil of 4M hydrogen chloride in dioxan. The solution was stirred at room temperature for 3.25

hours and then 25 ml of toluene was added and the solvents were evaporated. After three additional evaporations from 25 ml of toluene there was obtained 0.45 g of 4-[2(R)-[1(R or S)-carboxy-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine (diastereoisomer 1) in the form of a colourless gum that was used directly without further purification.

Example 19

In a manner analogous to that described in the first paragraph of Example 13, from 0.278 g of 4-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) there was obtained 0.151 g of 4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) in the form of a white solid; nmr (MeOD); 3.73-3.49 (m.9H); 3.34 (dd,1H,J = 11,5); 3.19-3.11 (m,1H); 2.74-2.66 (m,1H); 2.55 (s,4H); 1.57-1.49 (m,1H), 1.38-1.26 (m,1H); 1.12-1.03 (m,1H); 0.82-0.75 (m,6H); MS: 370 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 14(i)-(ii), from 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2(R)-pentane-tricarboxylateand N-bromomethylsuccinimide there was obtained 4-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) in the form of a white solid; MS: 460 $(M+H)^+$.

Example 20

In a manner analogous to that described in the first paragraph of Example 13, from 0.19 g of 4-[2(R)-[1-(R or S)-(benxyloxycarbamoyl)-2-(2-oxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) there was obtained 0.104 g of 4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(2-oxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 3.70-3.39 (m,8H); 3.36-3.17 (m,4H); 3.14-3.05 (m,1H); 2.57-2.48 (m,1H); 2.28-2.17 (m,2H); 1.96-1.84 (m,2H); 1.62-1.52 (m,1H); 1.58-1.24 (m,1H); 1.13-1.03 (m,1H); 0.83-0.75 (m,6H); MS: 356 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 14(i)-(ii), from 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2(R)-pentanetricarboxylate and N-bromomethylpyrrolidine there was obtained 4-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(2-oxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl] morpholine (diastereoisomer 1) in the form of a white solid; MS: 446 $(M+H)^+$.

Example 21

In a manner analogous to that described in the first paragraph of Example 13, from 0.335 g of 1-[2(R)-1-(R or S)-(benzyloxycarbamoyl)-2-(2-oxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) there was obtained 0.19 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(2-oxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 3.78-3.58 (m,3H); 3.53-3.33 (m,4H); 3.27-3.17 (m,2H); 2.63-2.54 (m,1H); 2.34-2.26 (m,2H); 2.03-1.93 (m,2H); 1.77-1.45 (m,7H); 1.43-1.30 (m,1H); 1.20-1.08 (m,1H); 0.93-0.83 (m,6H); MS: 354 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 14(i)-ii), from 1,2-benzyl 1-tert.butyl 4-methyl-1,1,2-(R)-pentanetricarboxylate and N-bromomethylpyrrolidine there was obtained 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(2-oxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]piperidine (diastereoisomer 1) in the form of a white solid; MS: 444 $(M+H)^+$.

Example 22

In a manner analogous to that described in the first paragraph of Example 1, from 0.226 g of 4-[2(R)-[1-(R or S)-carboxy-3-phthalimidopropyl]-4-methylvaleryl]morpholine there was obtained 0.065 g of 4-[2(R)-[1-(R or S)-(hydroxycarbamoyl)-3-phthalimidopropyl]-4-methylvaleryl]morpholine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.88-7.76 (m,4H); 3.86-3.50 (m,8H); 3.24-3.15 (m,1H); 2.32-2.23 (m,1H)-;1.99-1.89 (m,1H); 1.83-1.73 (m,1H); 1.66-1.57 (m,1H); 1.43-1.29 (m,1H); 1.17-1.09 (m,1H); 0.89-0.83 (m,6H); MS: 432 $(M+H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in Example 1(i)-(ii), from 0.65 g of an approximately 5:1 mixture of diastereoisomers of 2(R)-[1(R or S)-(tert.butoxycarbonyl)-3-phthalimidopropyl]-4-methylvaleric

acid and 0.17 ml of morpholine there was obtained 0.462 g of 4-[2(R)-[1(R or S)-carboxy-3-phthalimidopropyl]-4-methylvaleryl]morpholine in the form of a colourless gum which was used withour further purification.

Example 23

In a manner analogous to that described in Example 13, from 0.2 g of N,N-diethyl-2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleramide (diastereoisomer 1), prepared in a manner analogous to that described in Example 13(iii)-(iv), there was obtained, after purification of the product by flash chromatography using 3% methanol in dichloromethane for the elution, 0.085 g of N,N-diethyl-2(R)-[1-(Ror S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleramide (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.85-7.75 (m,4H); 3.97 (dd,J = 14,10,1H); 3.68-3.6 (m,1H); 3.57-3.48 (m,2H); 3.38 (q,J = 7,2H); 3.2 (dt,J = 12,4,1H); 2.84 (dt,J = 14,5, 1H); 1.67-1.59 (m,1H); 1.47-1.36 (m,1H); 1.26 (t,J = 8,3H); 1.25-1.16 (m,1H); 1.13 (t,J = 8,3H); 0.9 (d,J = 6,3H); 0.85 (d,J = 6,3H). MS: 404 $(M+H)^+$.

Example 24

In a manner analogous to that described in Example 1, from 0.16 g of 3-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]thiazolidine (diastereoisomer 1), prepared in a manner analogous to that described in Example 1(i)-(ii), there was obtained, after purification of the product by flash chromatography using 5% methanol in dichloromethane for the elution, 0.039 g of 3-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]thiazolidine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.86-7.75 (m,4H); 4.8 (d,J = 10,0.5H); 4.63 (d,J = 10,0.5H); 4.36 (d,J = 10,0.5H); 4.13-4.07 (m,0.5H); 4.03 (d,J = 10,0.5H); 3.87-3.72 (m,2H); 3.63-3.55 (m,0.5H); 3.45-3.36 (m,0.5H); 3.24-2.95 (m,2.5H); 1.62-1.54 (m,1H); 1.46-1.37 (m,1H); 1.29-1.2 (m,1H); 0.9 (d,J = 6,3H); 0.85 (d,J = 6,3H). MS: 420 $(M+H)^+$.

Example 25

In a manner analogous to that described in Example 13, from 0.25 g of N-ethyl-2(R)-[1(RS)-(bensyloxycarbamoyl)-2-phthalimidoethyl)-N,4-dimethylvaleramide (8:1 mixture of diastereoisomers), prepared in a manner analogous to that described in Example 13(iii)-(iv), there was obtained 0.083 g of N-ethyl-2(R)-[1(RS)-(hydroxycarbamoyl)-2-phthalimidoethyl)-N,4-dimethylvaleramide (8:1 mixture of diastereoisomers) in the form of a white solid; nmr (MeOD): 7.85-7.75 (m,4H); 3.95-3.83 (m,1H); 3.75-3.62 (m,1H); 3.4-3.08 (m,10H); 2.95-2.87 (m,1H); 2.83 (m,1H); 1.65-1.55 (m,1H); 1.43-1.33 (m,1H); 1.28-1.13 (m,2H); 1.03 (t,J = 6,2H); 0.89 (d,J = 6,3H); 0.85 (d,J = 6,3H). MS: 390 $(M+H)^+$.

Example 26

In a manner analogous to that described in Example 13, from 0.1 g of 4-[2(R)-[1(RS)-(benzyloxycarbamoyl)-5-phthalimidopentyl]-4-methylvaleryl]morpholine (5:1 mixture of diastereoisomers), prepared in a manner analogous to that described in Example 1(i)-(ii), there was obtained 0.045 g of 4-[2(R)-[1(RS)-(hydroxycarbamoyl)-5-phthalimidopentyl]-4-methylvaleryl]morpholine (3:1 mixture of diastereoisomers) as a cream coloured solid; nmr (MeOD): 7.85-7.75 (m,4H); 3.8-3.49 (m,12H); 3.15 (d,t,1H,J = 14,3); 2.18 (dt,1H,J = 12,3); 1.68-1.5 (m,4H); 1.38-1.05 (m,5H); 0.86-0.82 (m,6H). MS: 460 $(M+H)^+$.

Example 27

In a manner analogous to that described in Example 13, from 1.06 g of N-phenyl-2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-phthalimidoethyl]-N,4-dimethylvaleramide there was obtained, after purification by flash chromatography using 2% methanol in dichloromethane for the elution, 0.65 g of N-phenyl-2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-N,4-dimethylvaleramide as a white foam; nmr (MeOD): 7.75-7.68 (m,4H); 7.28-7.17 (m,4H); 7.08-7.04 (m,1H); 3.77 (dd,1H,J = 14,8); 3.69 (dd,1H,J = 14,7); 3.14 (s,3H); 2.78-2.65 (m,2H); 1.62-1.55 (m,1H); 1.42-1.32 (m,1H); 1.25-1.18 (m,1H); 0.7 (d,3H,J = 7); 0.54 (d,3H,J = 7); MS: 438 $(M+H)^+$.

The starting material was prepared as follows:

(i) A solution of 1.49 g 2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleric acid (6:1 mixture of diastereoisomer 1 and diastereoisomer 2) in 20 ml of toluene was cooled to -10°C. A few drops of N,N-dimethylformamide were added, followed by 0.34 ml of oxalyl chloride. The mixture was

stirred at -10 °C for 1 hour and then the solvent was evaporated under a high vacuum at 10 °C. The residue was redissolved in 10 ml of dichloromethane and cooled to 0 °C. 0.5 ml of triethylamine was added, followed by 0.4 nil of N-methylaniline. The mixture was stirred for 1 hour at 0 °C and allowed to warm to room temperature overnight. The solvent was evaporated and the residue was redissolved in 50 ml of ethyl acetate and washed successively with 5% sodium bicarbonate solution, 2N hydrochloric acid and saturated brine solution. The organic phase was dried over anhydrous magnesium sulphate and evaporated to give an orange oil. Purification by flash chromatography on silica gel using 3:1 hexane/ethyl acetate for the elution gave1.23 g of N-phenyl-2(R)-[1(R or S)-(tertbutoxy-carbonyl)-2-phthalimidoethyl]-N,4-dimethylvaleramide (diastereoisomer 1) as a pale yellow oil.; nmr ($CDCl_3$) 7.83-7.78 (m,2H); 7.73-7.68 (m,2H); 7.32-7.05 (m,5H); 4.0 (dd,1H,J = 13,9); 3.74 (dd,1H,J = 14,6); 3.26 (s,3H); 3.03-2.96 (m,1H); 2.83-2.76 (m,1H); 1.78-1.68 (m,1H); 1.57-1.46 (m,1H); 1.1 (s,9H); 0.87 (d,3H,J = 7); 0.65 (d,3H,J = 7). MS: 479 $(M + H)^+$.

(ii) In a manner analogous to Example 13 (iv) from 1.23 g of N-phenyl-2(R)-[1(R or S)-(tertbutoxycarbonyl)-2-phthalimidoethyl]-N,4-dimethylvaleramide there were obtained, after flash chromatography using 2% methanol in dichloromethane for the elution, 1.06 g of N-phenyl-2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-phthalimidoethyl]-N,4-dimethylvaleramide as a white foam; nmr ($CDCl_3$) 7.8-7.74 (m,4H); 7.45-7.28 (m,6H); 7.04-6.85 (m,4H); 4.96 (d,1H,J = 10); 4.89 (d,1H,J = 11); 3.95 (dd,1H,J = 14,6); 3.72 (dd,1H,J = 14,9); 3.17 (s,3H); 3.05-2.98 (m,1H); 2.64-2.58 (m,1H); 1.68-1.6 (m,1H); 1.49-1.32 (m,2H); 0.79 (d,3H,J = 6); 0.66 (d,3H,J = 6). MS: 528 $(M + H)^+$.

Example 28

In a manner analogous to that described in the first paragraph of Example 13, from 0.31 g of 1-[2(R)-[1-(R or S)-(benzyloxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-2(R)-pyrrolidinemethanol (diastereoisomer 1) there was obtained, after flash chromatography on silica gel using dichloromethane/methanol (15:1) for the elution and crystallization from ethyl acetate, 0.07 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-2(R)-pyrrolidine methanol (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.86-7.74 (m, 4H); 4.20-4.10 (m, 1H); 4.05-3.97 (m, 1H); 3.81-3.57 (n, 5H); 3.10-3.02 (m, 1H); 2.84-2.76 (m, 1H); 2.14-1.87 (m, 4H); 1.73-1.63 (m, 1H); 1.50-1.35 (m, 1H); 1.24-1.14 (m, 1H); 0.94-0.84 (m, 6H); MS: 432 $(M + H)^+$.

The starting material was prepared as follows:

In a manner analogous to that described in the second paragraph of Example 9, from 0.41 g of 1-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]-2(R)-pyrrolidinemethanol (diastereoisomer 1), prepared in a manner analogous to that described in Example 1(i), there was obtained 0.31 g of 1-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]-2(R)-pyrrolidinemethanol (diastereoisomer 1) in the form of a pale brown foam which was used without further purification

Example 29

In a manner analogous to that described in the first paragraph of Example 13, from 0.2 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-3(S)-(methylcarbamoyl)1-pyridazinecarboxylate (diastereoisomer 1) there was obtained, after flash chromatography on silica gel using dichloromethane/methanol (20:1) for the elution, 0.044 g of hexahydro-2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-N-methyl-3(S)-pyridazinecarboxamide (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.83-7.69 (m, 4H); 5.06 (m, 1H); 3.99 (dd, 1H, J = 14,9); 3.57 (dd, 1H, J = 14,5); 3.04-2.95 (m, 1H); 2.86-2.74 (m, 2H); 2.70 (s, 3H); 2.07-1.86 (m, 2H); 1.68-1.35 (m, 5H); 1.18-1.10 (m, 1H); 0.88 (d, 3H, J = 5.5); 0.80 (d, 3H, J = 6.0); MS: 474 $(M + H)^+$.

The starting material was prepared as follows:

(i) In a manner analogous to that described in Example 27(i), from 1.02 g of 2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleric acid (6:1 mixture of diastereoisomer 1 and diastereoisomer 2) and 0.7 g of hexahydro-1-(benzyloxycarbonyl)-(3S)-pyridazinecarboxylic acid there was obtained, after chromatography on silica gel using ether/hexane (1:4) followed by ethyl acetate for the elution, 0.6 g of hexahydro-1-(benzyloxycarbonyl)-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]-3(S)-pyridazinecarboxylic acid in the form of a colourless gum.

(ii) A solution of 0.6 g of hexahydro-1-(benzyloxycarbonyl)-2[2(R)-[1(Ror S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]-3(S)-pyridazinecarboxylic acid in 5 ml of dimethylformamide was cooled to 0 °C and 0.27 g of 1-hydroxybenzotriazole and 0.36 g of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride were added. After 40 minutes 0.4 ml of a 40% aqueous solution of

methylamine was added and the mixture was stirred for 2.5 hours. The solvent was evaporated and the residue was treated with 20 ml of 5% aqueous sodium hydrogen carbonate solution. The product was extracted with ethyl acetate and the extract was washed with 5% citric acid and aqueous sodium chloride solution. After drying over anhydrous magnesium sulphate the solvent was evaporated to give 0.638 g of a colourless gum which was purified by flash chromatography using ether/hexane (3:1) for the elution. There was obtained 0.467 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in the form of a colourless gum.

(iii) In a manner analogous to Example 13(iv) from 0.23 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate there was obtained 0.2 g of benzyl hexahydro-2-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in the form of a white solid.

Example 30

In a manner analogous to that described in the first paragraph of Example 1 and part (ii) of Example 1, from 0.273 of benzyl hexahydro-2-[2(R)-[1(R or S)-(tert.butoxycarbonyl)-2-phthalimidoethyl]-4-methylvaleryl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate there was obtained 0.12 g of benzyl hexahydro-2-[2(R)-[R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-3(S)-(methylcarbamoyl)-1-pyridazinecarboxylate in the form of a white solid; MS: 608 $(M+H)^+$.

Example 31

In a manner analogous to that described in the first paragraph of Example 13, from 0.185 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-N-methyl-2(S)-piperidinecarboxamide there was obtained, after purification by flash chromatography on silica gel using dichloromethane/methanol (16:1) for the elution, 0.06 mg of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-N-methyl-2(S)-piperidinecarboxamide (diastereoisomer 1) in the form of a white solid; MS: 473 $(M+H)^+$.

Example 32

In a manner analogous to that described in the first paragraph of Example 1, from 0.22 g of 1-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]-4-methoxypiperidine (diasteroisomer 1), prepared in a manner analogous to that described in Example 1 (i)-(ii), there was obtained 0.108 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-4-methoxypiperidine (diasteroisomer 1) in the form of a white solid; nmr (MeOD): 7.86-7.74 (m, 4H); 4.05-3.83 (m, 2.5H); 3.70-3.44 (m, 3.5H); 3.41-3.27 (m, 4.5H); 3.10-3.01 (m, 0.5H); 2.97-2.90 (m, 1H); 2.10-2.00 (m, 0.5H); 1.94-1.84 (m, 1H); 1.80-1.68 (m, 1H); 1.66-1.31 (m, 3.5H); 1.21-1.13 (m, 1H); 0.92-0.82 (m, 6H); MS: 446 $(M+H)^+$.

Example 33

In a manner analogous to that described in the first paragraph of Example 1, from 0.44 g of 1-[2(R)-[1(R or S)-carboxy-2-phthalimidoethyl]-4-methylvaleryl]-4-piperidinone, prepared in a manner analogous to that described in Example 1 (ii)-(iii), there was obtained 0.157 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-4-piperidinone oxime (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.86-7.75 (m, 4H); 3.92-3.76 (m, 3H); 3.72-3.58 (m, 2H); 3.38-2.82 (m, 3H); 2.71-2.25 (m, 4H); 1.66-1.57 (m, 1H); 1.48-1.34 (m, 1H); 1.26-1.17 (m, 1H); 0.92-0.82 (m, 6H); MS: 445 $(M+H)^+$.

Example 34

In a manner analogous to that described in the first paragraph of Example 13, from 0.32 g of N-[2(R)-[1-(R or S)-(benzyloxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-L-proline methyl ester (diastereoisomer 1), prepared in a manner analogous is that described in Example 13 (iii)-(iv), there was obtained 0.13 g of N-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-L-prolinemethyl ester (diasteroisomer 1) in the form of a white solid; nmr (MeOD): 7.86-7.77 (m, 4H); 3.95-3.84 (m, 2H); 3.78 (d, 2H, J=8); 3.69-3.61 (m, 1H); 3.60 (s, 3H); 3.11-3.04 (m, 1H); 3.00-2.92 (m, 1H); 2.21-2.12 (m, 1H); 2.10-1.95 (m, 2H); 1.90-1.82 (m, 1H); 1.74-1.63 (m, 1H); 1.60-1.52 (m, 1H); 1.22-1.14 (m, 1H); 0.94 (d, 3H, J=6); 0.86

(d, 3H, J = 6); MS: 460 $(M+H)^+$.

Example 35

In a manner analogous to that described in the first paragraph of Example 13, from 1.116 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1), prepared in a manner analogous to that described in Example 14 (i)-(ii), there was obtained 0.785 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 4.24-4.01 (m, 2H); 3.93-3.81 (m, 1H); 3.78-3.64 (m, 1H); 3.52-3.22 (m, 4H); 3.10-2.81 (m, 4H); 2.02-1.77 (m, 2H); 1.67-1.26 (m, 10H); 1.19-1.09 (m, 1H); 0.93-0.82 (m, 6H); MS: 427 $(M+H)^+$.

Example 36

In a manner analogous to that described in the first paragraph of Example 1, from 1.55 g of 1-[2(R)-1(R or S)-carboxy-2-(tetrahydro-2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl)ethyl]-4-methylvaleryl]-4-piperidine (diastereoisomer 1) there was obtained 0.572 g of 1-[2(R)-1(R or S)-(hydroxycarbamoyl)-2-(tetrahydro-2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl)ethyl]-4-methylvaleryl]-4-piperidine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 3.70-3.46 (m, 4H); 3.42-3.29 (m, 2H); 3.25-3.15 (m, 4H); 2.89-2.76 (m, 1H); 1.68-1.27 (m, 8H); 1.27-1.04 (m, 1H); 0.83-0.76 (m, 6H); MS: 385 $(M+H)^+$.

The starting material was prepared as follows:

(i) In a manner analogous to that described in Example 18(i)-(ii), from 4.76 g of 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2 (R)-pentanetricarboxylate and 2.05 g of 4-bromomethyl-2-tetrahydro-2-methyl-3,5-dioxo-1,2,4-oxadiazole there was obtained 1.55 g of 1-[2(R)-1(R or S)-carboxy-2-(tetrahydro-2-methyl-3,5-dioxo-1,2,4-oxadiazol-4-yl)ethyl]-4-methylvaleryl]-4-piperidine (diastereoisomer 1) in the form of a gum which is used without further purification.

Example 37

In a manner analogous to that described in the first paragraph of Example 13, from 0.184 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3-methyl-2,4,5-trioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1), prepared in a manner analogous to that described in Example 14(i)-(ii) from 1,2-dibenzyl 1-tert.butyl 4-methyl-1,1,2 (R)-pentanetricarboxylate and 1-bromomethyl-3-methyl-2,4,5-trioxo-1-imidazole, there was obtained 0.08 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3-methyl-2,4,5-trioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1) in the form of a white solid; nmr (MeOD) 4.20-3.95 (m, 2H); 3.93-3.75 (m, 2H); 3.57-2.97 (m, 7H); 2.90-2.81 (m, 1H); 2.02-1.76 (m, 2H); 1.66-1.29 (m, 4H); 1.20-1.12 (m, 1H); 0.91-0.82 (m, 6H); MS: 413 $(M+H)^+$.

Example 38

In a manner analogous to that described in the first paragraph of Example 13, from 0.261 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(2,5-dioxo-3-phenyl-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1), prepared in a manner analogous to that described in Example 14(i)-(ii), there was obtained 0.169 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(2,5-dioxo-3-phenyl-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 7.60-7.55 (m, 2H); 7.35-7.29 (m, 2H); 7.12-7.05 (m, 1H); 4.37-4.24 (m, 2H); 4.19-3.92 (m, 2H); 3.89-3.66 (m, 2H); 3.54-2.84 (m, 5H); 1.99-1.71 (m, 2H); 1.64-1.23 (m, 4H); 1.17-1.08 (m, 1H); 0.88-0.78 (m, 6H); MS: 461 $(M+H)^+$.

Example 39

In a manner analogous to that described in the first paragraph of Example 13, from 0.146 g of 4-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3-methyl-2,4,5-trioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1), prepared in a manner analogous to that described in Example 14(i)-(ii), there was obtained 0.085 g of 4-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3-methyl-2,4,5-trioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]morpholine (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 3.86-3.54 (m. 10H); 3.28-3.20 (m, 1H); 3.08 (s, 3H); 2.91-2.82 (m, 1H); 1.66-1.57 (m, 1H); 1.48-1.36 (m, 1H); 1.23-1.15 (m, 1H); 0.89-0.84 (m, 6H); MS: 399 $(M+H)^+$.

Example 40

In a manner analogous to that described in the first paragraph of Example 13, from 0.363 g of N^2-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-N^1-methyl-L-prolinamide (diastereoisomer 1), prepared in a manner analogous to that described in Example 14-(i)-(ii), there was obtained 0.234 g of N^2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-N^1-methyl-L-prolinamide (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 4.35-4.29 (m, 1H); 3.92-3.83 (m, 1H); 3.74-3.58 (m, 2H); 3.47-3.41 (m, 1H); 3.10-3.01 (m, 1H); 2.88-2.75 (m, 4H); 2.59 (s, 3H); 2.26-1.84 (m, 4H); 1.74-1.55 (m, 2H); 1.34 (s, 3H); 1.32 (s, 3H); 1.18-1.11 (m, 1H); 0.92 (d, 3H, J = 5.5); 0.86 (d, 3H, J = 6); MS: 454 $(M + H)^+$.

Example 41

In a manner analogous to that described in the first paragraph of Example 13, from 0.3 g of 1-[2(R)-[1(R or S)-(benzyloxycarbamoyl)-2-(2-oxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1), prepared in a manner analogous to that described in Example 14(i)-(ii), there was obtained 0.116 g of 1-[2-(R)-[1(R or S)-(hydroxycarbamoyl)-2-(2-oxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 4.16-3.91 (m, 2H); 3.84-3.73 (m, 1H); 3.43-2.97 (m, 7H); 2.56-2.45 (m, 1H); 2.27-2.18 (m, 2H); 1.96-1.70 (m, 4H); 1.61-1.19 (m, 4H); 1.11-1.01 (m, 1H) 0.84-0.72 (m, 6H); MS: 370 $(M + H)^+$.

Example 42

In a manner analogous to that described in the first paragraph of Example 13, from 0.16 g of 1-[2(R)-1-(R or S)-(benzyloxycarbamoyl)-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1), prepared in a manner analogous to that described in Example 14(i)-(ii), there was obtained 0.048 g of 1-[2(R)-1(R or S)-(hydroxycarbamoyl)-2-(2,5-dioxo-1-pyrrolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer1) in the form of a white solid; nmr (MeOD): 4.25-4.01 (m, 2H); 3.94-3.80 (m, 1H); 3.78-3.63 (m, 1H); 3.52-3.02 (m, 4H); 2.82-2.73 (m, 1H); 2.63 (d, 4H, J = 6); 2.04-1.76 (m, 2H); 1.64-1.27 (m, 4H); 1.18-1.09 (m, 1H); 0.92-0.80 (m, 6H); MS: 384 $(M + H)^+$.

Example 43

In a manner analogous to that described in the first paragraph of Example 13, from 0.43 g of 1-[2(R)-[1-(R or S)-(benzyloxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diasteroisomer 1), prepared in a manner analogous to that described in Example 14(i)-(ii), there was obtained 0.158 g of 1-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol (diastereoisomer 1) in the form of a white solid; nmr (MeOD): 4.25-3.97 (m, 2H); 3.93-3.79 (m, 2H); 3.74-3.61 (m, 1H); 3.52-2.97 (m, 4H); 2.93-2.80 (m, 4H); 2.02-1.76 (m, 2H); 1.67-1.27 (m, 4H); 1.19-1.10 (m, 1H); 0.91-0.80 (m, 6H); MS: 399 $(M + H)^+$.

The following Examples illustrate pharmaceutical preparations containing the hydroxamic acid derivatives provided by the present invention:

Example A

Tablets containing the following ingredients may be produced in a conventional manner:

Ingredient	Per Tablet
Hydroxamic acid derivative	10.0 mg
Lactose	125.0 mg
Corn starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg
Total weight	215.0 mg

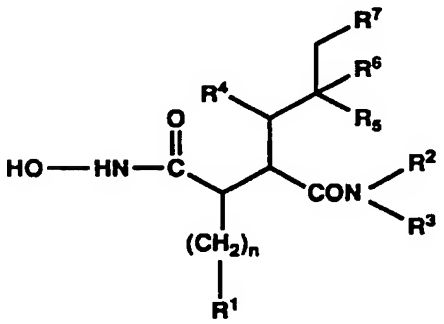
Example B

Capsules containing the following ingredients may be produced in a conventional manner:

Ingredient	Per Capsule
Hydroxamic acid derivative	10.0 mg
Lactose	165.0 mg
Corn starch	20.0 mg
Talc	5.0 mg
Capsule fill weight	200.0 mg

Claims

1. Compounds of the general formula



(I)

wherein

R^1 represents a 5- or 6-membered N-heterocyclic ring which (a) is attached via the N atom, (b) optionally contains N, O and/or S as additional hetero atom(s) in a position or positions other than adjacent to the linking N atom, (c) is substituted by oxo on one or both C atoms adjacent to the linking N atom and (d) is optionally benz-fused or optionally substituted on one or more other C atoms by lower alkyl or oxo and/or on any additional N atom(s) by lower alkyl or aryl;

R^2 represents lower alkyl and R^3 represents lower alkyl or aryl, or

NR^2R^3 represents a saturated 5-, 6- or 7-membered heterocyclic ring which optionally contains $-NR^a$, -O-,-S-, -SO- or $-SO_2-$ as a ring member and/or which is optionally substituted by hydroxy, lower alkoxy, oxo, ketalized oxo, amino, mono(lower alkyl)amino, di(lower alkyl)amino, carboxy, lower alkoxycarbonyl, hydroxymethyl, lower alkoxymethyl, carbamoyl, mono(lower alkyl)carbamoyl, di(lower alkyl)carbamoyl or hydroxyimino;

R^a represents hydrogen, lower alkyl, lower alkanoyl, aryl-lower alkanoyl, lower alkoxycarbonyl, aryl-lower alkoxycarbonyl or mono(lower alkyl)carbamoyl;

R^4, R^5, R^6 and R^7 each represent hydrogen or methyl, provided that at least two of these symbols represent hydrogen; and

n stands for 1-4;

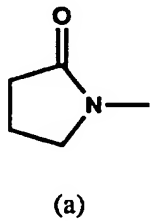
and pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein R^1 represents a 5- or 6-membered N-heterocyclic ring which (a) is attached via the N atom, (b) optionally contains N, O and/or S as additional hetero atom(s) in a position or positions other than adjacent to the linking N atom, (c) is substituted by oxo on one or both

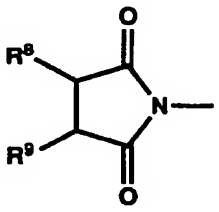
C atoms adjacent to the linking N atom and (d) is optionally benz-fused or optionally substituted on one or more other C atoms by lower alkyl or oxo and/or on any additional N atom(s) by lower alkyl; R^2 represents lower alkyl and R^3 represents lower alkyl or aryl or NR^2R^3 represents a saturated 5-, 6- or 7-membered heterocyclic ring which optionally contains $-NR^a-$, -O-, -S-,-SO- or $-SO_2-$ as a ring member and/or which is optionally substituted by hydroxy, lower alkoxy, oxo, ketalized oxo, amino, mono(lower alkyl)amino, di(lower alkyl)amino, carboxy, lower alkoxycarbonyl, hydroxymethyl, lower alkoxymethyl, carbamoyl, mono(lower alkyl)carbamoyl or di(lower alkyl)carbamoyl; R^a represents hydrogen or lower alkyl; and R^4, R^5, R^6, R^7 and n have the significance given in claim 1.

3. Compounds according to claim 1 or claim 2, wherein the N-heterocyclic ring R^1 optionally contains as additional hetero atom(s) one or two N atoms, one N atom and one O atom or one O atom.

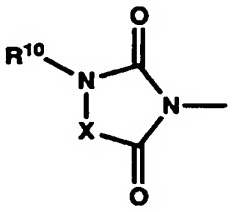
4. Compounds according to claim 3, wherein R^1 represents a ring of the formula



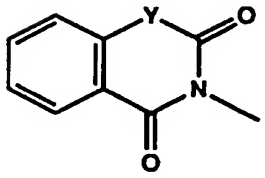
(a)



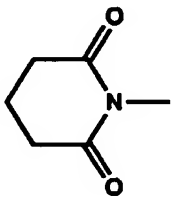
(b)



(c)

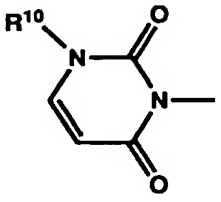


(d)



(e)

and



(f)

in which

R^8 and R^9	each represent hydrogen or together represent an additional bond or the remainder of a fused benzene ring;
R^{10}	represents hydrogen, lower alkyl or aryl;
X	represents -CO-, $-CH_2-$, -CH(lower alkyl)-, $-C(\text{lower alkyl})_2-$, -NH-, -N(lower alkyl)- or -O-; and
Y	represents -O-,-NH- or -N(lower alkyl)-.

5. Compounds according to claim 4, wherein R^{10} represents hydrogen or lower alkyl.

6. Compounds according to claim 4 or claim 5, wherein R^1 represents a ring of formula (b) or (c).

7. Compounds according to claim 6, wherein R^1 represents phthalimido, 1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl, 3-methyl-2,5-dioxo-1-imidazolidinyl or 3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl.

8. Compounds according to any one of claims 1-7, wherein NR^2R^3 represents a 5-, 6- or 7-membered saturated heterocyclic ring.

9. Compounds according to claim 8, wherein NR^2R^3 represents a 6-membered saturated heterocyclic ring.

10. Compounds according to claim 9, wherein NR^2R^3 represents morpholino, tetrahydro-1,4-thiazin-4-yl or 4-hydroxypiperidino.

11. Compounds according to any one of claims 1-10, wherein R^4, R^5 and R^7 each represent hydrogen and R^6 represents methyl.

12. Compounds according to any one of claims 1-11, wherein n stands for 1 or 2.

13. 4-[2-(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]morpholine.

14. 4-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]tetrahydro-1,4-thiazine.

15. 1-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-4-piperidinol.

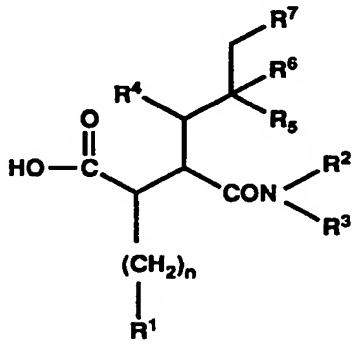
16. 1-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-(1,2-dimethyl-3,5-dioxo-1,2,4-triazolidin-4-yl)ethyl]-4-methylvaleryl]piperidine.

17. 4-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-(3-methyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-tetrahydro-1,4-thiazine.

18. Hexahydro-2-[2(R)-[1(R or S)-(hydroxycarbamoyl)-2-phthalimidoethyl]-4-methylvaleryl]-N-methyl-3(S)-pyridazinecarboxamide.

19. 1-[2(R)-[1(R or S)-(Hydroxycarbamoyl)-2-(3,4,4-trimethyl-2,5-dioxo-1-imidazolidinyl)ethyl]-4-methylvaleryl]-4-piperidinol.

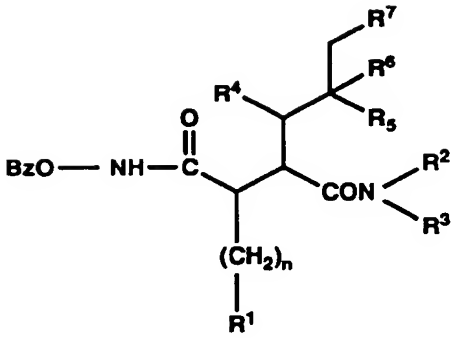
20. Compounds of the general formula



(II)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and n have the significance given in claim 1.

21. Compounds of the general formula



(IV)

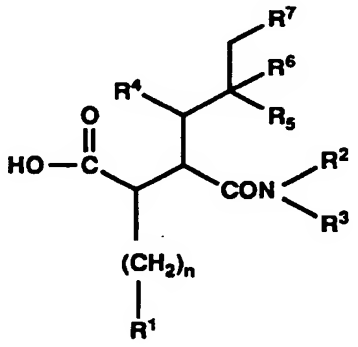
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and n have the significance given in claim 1 and Bz represents benzyl.

22. Compounds according to any one of claims 1-19 for use as therapeutically active substances.

23. Compounds according to any one of claims 1-19 for use in the control or prevention of degenerative joint diseases or in the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

24. A process for the manufacture of the compounds claimed in any one of claims 1-19, which process comprises

(a) reacting an acid of the general formula



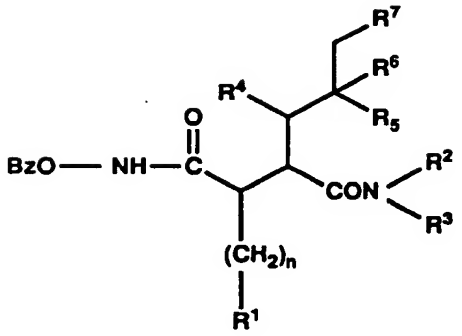
(II)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and n have the significance given in claim 1,
with a compound of the general formula

$H_2N\text{-}OZ$ (III)

wherein Z represents hydrogen, tri(lower alkyl)silyl or diphenyl(lower alkyl)silyl,
and, where required, cleaving off any diphenyl(lower alkyl)silyl group present in the reaction product, or

(b) catalytically hydrogenating a compound of the general formula



(IV)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and n have the significance given in claim 1 and Bz represents benzyl,

and,

if desired, converting a compound of formula I obtained into a pharmaceutically acceptable salt.

25. A medicament containing a compound according to any one of claims 1-19 and a therapeutically inert carrier material.

26. A medicament for the control or prevention of degenerative joint diseases or for the treatment of invasive tumours, atherosclerosis or multiple sclerosis, containing a compound according to any one of claims 1-19 and a therapeutically inert carrier material.

27. The use of a compound according to any one of claims 1-19 in the control or prevention of illnesses.

28. The use of a compound according to any one of claims 1-19 for the control or prevention of degenerative joint diseases or for the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

29. The use of a compound according to any one of claims 1-19 for the manufacture of a medicament for the control or prevention of degenerative joint diseases or for the treatment of invasive tumours, atherosclerosis or multiple sclerosis.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 10 8628

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	WO-A-9 005 716 (BRITISH BIO-TECHNOLOGY LTD.) * claims * ---	1,26	C07D209/48 A61K31/395 C07D401/06 C07D491/10
A	US-A-4 743 587 (G.D. SEARLE & CO.) * claims * -----	1,26	C07D249/12 C07D211/88 C07D233/72 C07D207/40 C07D207/26 C07D417/06 C07D403/12 C07D271/06 C07D233/96 C07D403/06 //(C07D491/10, 317:00,209:00)

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	27 SEPTEMBER 1993	VAN BIJLEN H.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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L : document cited for other reasons

& : member of the same patent family, corresponding document

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